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Determinants and Correlates of Target Lesion Calcium in Coronary Artery Disease: A Clinical, Angiographic and Intravascular Ultrasound Study

GARY S. MINTZ, MD, FACC, AUGUSTO D. PICHARD, MD, FACC, JEFFREY J. POPMA, MD, FACC, KENNETH M. KENT, MD, PHD, FACC, LOWELL F. SATLER, MD, FACC, THERESA A. BUCHER, RN, MARTIN B. LEON, MD, FACC

Washington, D.C.

Objectives. **This report used intravascular ultrasound and quantitative coronary angiography to explore the relation between lesion-associated calcium and risk factors, clinical presentation and angiographic severity of coronary artery stenoses.**

Background. **Coronary artery calcium is a marker for significant coronary atherosclerosis. Noninvasive procedures are being proposed as screening tests for coronary artery disease. Intravascular ultrasound identification of tissue calcium has been validated in vitro.**

Methods. **Independent chart review, preintervention intravascular ultrasound imaging and coronary angiography were used to study primary native vessel lesions in 1,442 patients. Target lesions and reference segments were evaluated according to previously published quantitative and qualitative methods. Results are presented as mean value ± SD.**

Results. **Overall, 1,043 lesions contained target lesion calcium (72%); the arc of target lesion calcium was 110 ± 109°. Lesions with an ultrasound plaque burden >0.75 or an angiographic diameter stenosis >0.25 had a prevalence of calcium of at least 65%, with a mean arc >100°. Intermediate lesions had as much target lesion calcium as did angiographically severe lesions.**

Using multivariate linear regression analysis, patient age, stable (vs. unstable) angina and the intravascular ultrasound lesion site and reference segment plaque burden (but not the angiographic diameter stenosis) were the independent predictors of the arc of target lesion calcium (all $p < 0.0001$).

Conclusions. **Intravascular ultrasound analysis shows that coronary calcification correlates with plaque burden but not with degree of lumen compromise. Thus, the noninvasive detection of coronary calcium is predictive of future cardiac events, presumably because coronary calcification is a marker for overall atherosclerotic plaque burden. Coronary calcium increases with increasing patient age and is less common in unstable lesion subsets.**

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Pathologic studies (1–9) have showed that lesion-associated coronary artery calcium increases with the extent and severity of atherosclerosis, increasing patient age and the presence of primary or secondary chronic hypercalcemia or hyperlipidemia or chronic renal insufficiency. Because coronary artery calcium is a marker for significant coronary atherosclerosis, noninvasive procedures are being proposed as screening tests for coronary artery disease (10–13). Two recent reports (14,15) have indicated that patients with high coronary artery calcium scores are at an increased risk for coronary events.

The intravascular ultrasound identification of tissue calcium has been validated in vitro (16–18,20). Calcium has a characteristic acoustic signature: brighter than the reference adventitia, with shadowing of deeper arterial structures. Intravascular ultrasound detection of target lesion calcium approaches the highest pathologic incidence (79%) reported (3). The present report used intravascular ultrasound and quantitative coronary angiography to explore the relation between lesion-associated calcium and risk factors, clinical presentation and angiographic severity of coronary artery stenoses.

Methods

Patient and lesion demographics. We used preintervention intravascular ultrasound imaging and coronary angiography to study primary native vessel lesions in 1,442 patients (1,114 men, 328 women; mean [±SD] age 61 ± 11 years, range 30 to 92). Previously treated lesions were excluded. Both primary (presumed culprit) and secondary lesions were evaluated, thus permitting interlesional comparison. Lesion location was the left main coronary artery in 75, left anterior descending coronary artery in 570, left circumflex coronary artery in 261 and right coronary artery in 536; 93 lesions were aorto-ostial.

From the Intravascular Ultrasound Imaging and Cardiac Catheterization Laboratories, Washington Hospital Center, Washington, D.C. This study was supported in part by the Medlantic Research Institute and the Cardiology Research Foundation, Washington, D.C.

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Address for correspondence: Dr. Martin B. Leon, Director of Research, Washington Cardiology Center, 110 Irving Street NW, Suite 4B1, Washington, D.C. 20010.

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Abbreviations and Acronyms
ECG = electrocardiographic
TIMI = Thrombolysis in Myocardial Infarction

Clinical and lesion demographics. To obtain clinical demographics and laboratory results, the hospital charts of all patients were reviewed independently by a registered nurse (T.A.B.) who had no knowledge of the angiographic and intravascular ultrasound findings. Angina was tabulated as *stable* (including progressive symptoms without rest electrocardiographic [ECG] changes) or *unstable* (requiring documented rest ECG changes and included postinfarction angina).

Angiographic analysis. All cineangiograms were analyzed by a core angiographic laboratory in blinded manner with regard to the ultrasound and clinical findings. The following qualitative and quantitative angiographic techniques and definitions represent standard methodology. All have been published previously (21).

Quantitative analysis. Using a computer-assisted, automated edge detection algorithm (ARTREK, Quantitative Cardiac Systems) and the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter in diastole before intervention was measured from multiple projections, and the results from the "worst" view were recorded. The reference segment diameter was averaged from user-defined 5-mm long angiographically normal segments proximal and distal to the lesion but between any major side branches. Lesion length was measured as the distance (in mm) from the proximal to the distal shoulder of the lesion in the projection that demonstrated the lesion with the least amount of foreshortening. Target lesions were then divided into four groups according to degree of angiographic diameter stenosis: 1) ≤0.25; 2) 0.26 to 0.50; 3) 0.51 to 0.75; and 4) 0.76 to 1.00.

Qualitative analysis. For the purpose of this study, *ostial lesions* were within 3 mm of the coronary ostia. An *eccentric target lesion* appeared to have three times as much plaque on one side of the lesion as on the other. *Angulation* was present if the centerline through the lumen proximal to the lesion compared with the centerline through the lumen distal to the lesion was >45°. A *tortuous artery* had at least two bends >60° that had to be traversed to reach the target lesion. *Flow* was graded according to Thrombolysis in Myocardial Infarction (TIMI) study criteria; TIMI flow grade 0 or 1 was considered representative of a total occlusion.

Intravascular ultrasound imaging protocol. All intravascular ultrasound studies were performed before any intervention and only after administration of 200 μg of intracoronary nitroglycerin. The intravascular ultrasound studies were performed using one of three commercially available systems. The first system (InterTherapy/Cardiovascular Imaging Systems) incorporated a single-element 25-MHz transducer and an angled mirror mounted on the tip of a flexible shaft that was rotated at 1,800 rpm within a 3.9F short monorail polyethylene imaging sheath to form planar cross-sectional images in real time. The second system (Cardiovascular Imaging Systems) incorporated a single-element 30-MHz beveled transducer within either a 2.9F long monorail imaging catheter having a common distal lumen design (the distal lumen alternatively accommodates the imaging core or the guide wire but not both) or a 3.2F short monorail imaging catheter. With both of these systems, the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence. The third system (Hewlett-Packard and Boston Scientific) incorporated a single-element 30-MHz beveled transducer rotated at 1,800 rpm within a 3.5F short monorail imaging catheter; with this system, the catheter was advanced or withdrawn manually with fluoroscopic guidance to perform the imaging sequence. Regardless of the system used, the catheter was advanced ~10 mm distal to the lesion, the videorecorder turned on and transducer withdrawn automatically or manually until it reached the aorto-ostial junction. Intravascular ultrasound studies were recorded on 0.5-in. high resolution s-VHS tape for off-line analysis.

All intravascular ultrasound studies have the ongoing approval of the Washington Hospital Center Institutional Review Board, and all patients provided informed consent.

Intravascular ultrasound analysis. Validation of normal coronary artery anatomy, plaque composition and measurements of external elastic membrane cross-sectional area, lumen cross-sectional area and plaque plus media cross-sectional area by intravascular ultrasound have been previously reported (16–20,22–24). The external elastic membrane cross-sectional area, which represents the border between the hypoechoic media and the hyperechoic adventitia, has been shown to be a reproducible measure of total arterial cross-sectional area. Cross-sectional narrowing has also been called the plaque burden or percent plaque area by other investigators.

Using computer planimetry, the target lesions and reference segments were analyzed using the following measurements (Fig. 1): 1) lesion site external elastic membrane cross-sectional area (mm^2); 2) lesion site lumen cross-sectional area (mm^2); 3) plaque plus media cross-sectional area (mm^2) equal to external elastic membrane cross-sectional area minus lumen cross-sectional area (mm^2); 4) cross-sectional narrowing equal to plaque plus media cross-sectional area divided by the external elastic membrane cross-sectional area.

The lesion site selected for analysis was the image slice with the smallest lumen cross-sectional area; if there were several image slices with an equally small lumen cross-sectional area, the lesion site selected for analysis had the largest external elastic membrane cross-sectional area and plaque plus media cross-sectional area. The reference segment was the most visually normal cross section within 10 mm proximal to the lesion but distal to any major side branch; a distal reference was used for ostial lesions (25). These methods for selecting the lesion site and reference segment for analysis and for measuring the external elastic membrane, lumen and plaque plus media cross-sectional area have been used extensively to study the acute and chronic effects of balloon and new-device

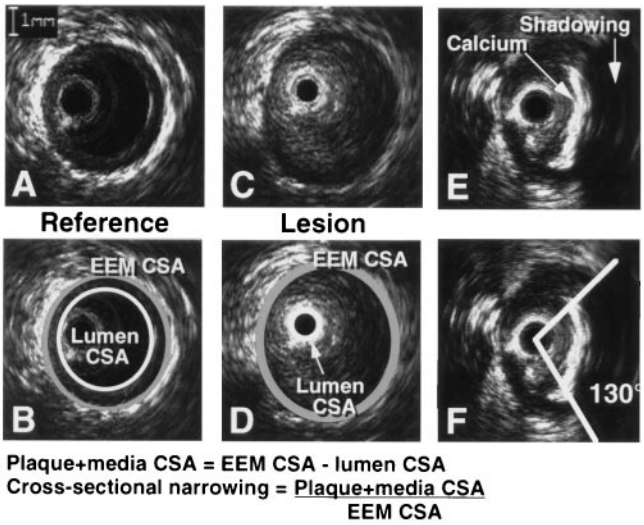

Figure 1. Illustration of intravascular ultrasound measurements. A reference segment is shown in **A** and **B**. The external elastic membrane (EEM) cross-sectional area (CSA) is indicated by the **gray oval**; the lumen cross-sectional area is indicated by the **white oval**. Similarly, a lesion is shown in **C** and **D**. The formulas for calculation of plaque plus media cross-sectional area and cross-sectional narrowing are shown. **E** and **F** illustrate calcification. Calcium is brighter than the reference adventitia with acoustic shadowing of deeper arterial structures **(E)**. The arc of calcium is measured with a protractor **(F)**.

angioplasty; these methods have been described elsewhere (25–31).

Target lesions were then classified into four groups according to lesion cross-sectional narrowing [1) ≤0.50; 2) 0.51 to 0.75; 3) 0.76 to 0.90; and 4) 0.91 to 1.00] and two groups according to reference segment cross-sectional narrowing [1) ≤0.50, and 2) >0.51].

Target lesion plaque composition was assessed visually to identify calcium (Fig. 1). The largest arc of calcium within any individual lesion was measured (in degrees) with a protractor centered on the lumen (26,27).

Although acoustic shadowing caused by lesion calcification at times made identification of the external elastic membrane difficult, two types of extrapolation were useful. Briefly, because the cross-sectional geometry of the coronary artery was more or less circular, extrapolation of the circumference of the external elastic membrane was possible provided that each calcific deposit did not shadow >60° of the adventitial circumference. Also, real-time axial movement of the transducer just distal and proximal to a calcific deposit (or to find the smallest circumferential arc of calcium within a larger calcific deposit) helped to unmask and fill in contiguous parts of the adventitia that were otherwise shadowed by that deposit. These methods have also been described previously (28–31).

Multilesion analysis. A second lesion was analyzed in 521 patients. This secondary lesion was compared with the primary lesions to assess the between-lesion differences in target lesion calcium.

Statistics. Statistical analysis was performed using StatView 4.02 (Abacus Concepts) or SAS (Statistical Analysis Systems, SAS Institute Inc.). Results are presented as mean value ± SD. Categoric data were compared using chi-square analysis. Continuous variables were compared using a Student unpaired *t* test or factorial analysis of variance and post hoc analysis with the Fisher protected least significant difference. A p value ≤0.05 was considered significant.

Univariate and multivariate linear regression analysis were used to select the best clinical, qualitative and quantitative angiographic or intravascular ultrasound predictors of the arc of target lesion calcium. Univariate predictors of the arc of target lesion calcium with a p value ≤0.2 were then entered into the multivariate model. Forward stepping was used to determine the best predictors of the arc of target lesion calcium.

Table 1. Interlesion Comparison in Intravascular Ultrasound Calcification (in 521 patients with two lesions imaged)

	Presence of Calcium in Lesion 1	
Presence of Calcium in Lesion 2	Yes [no. (%)]	No [no. (%)]
Yes	62 (12)	88 (17)
No	90 (17)	281 (54)

Results

Overall angiographic results. The reference lumen dimension measured 3.07 ± 0.76 mm; minimal lumen diameter measured 1.01 ± 0.61 mm; and diameter stenosis was calculated to be 65 ± 19%. Lesion length measured 8.3 ± 5.8 mm.

Overall intravascular ultrasound results. Overall, 1,043 lesions contained target lesion calcium (72%); the arc of target lesion calcium was 110 ± 109°.

The lesion site external membrane cross-sectional area measured 17.6 ± 6.6 mm^2; lumen cross-sectional area measured 2.7 ± 2.7 mm^2; plaque plus media cross-sectional area measured 14.9 ± 6.3 mm^2; and cross-sectional narrowing measured 84 ± 13%. Angiographic diameter stenosis correlated only fairly with ultrasound lesion cross-sectional narrowing ($r = 0.534$, $p < 0.0001$).

The reference segment external membrane cross-sectional area measured 18.4 ± 9.1 mm^2; lumen cross-sectional area measured 9.7 ± 5.6 mm^2; plaque plus media cross-sectional area measured 8.1 ± 9.7 mm^2; and cross-sectional narrowing measured 43 ± 14%.

Multilesion analysis. In the 521 patients in whom a second lesion was analyzed, there was a significant interlesion difference in the presence of target lesion calcification ($p < 0.0001$) (Table 1). In addition, there was only a weak, but significant interlesion correlation in the arcs of target lesion calcium ($r = 0.278$, $p < 0.0001$).

Relation of target lesion calcium to angiographic lesion severity. Lesions with an angiographic diameter stenosis >0.25 had a prevalence of calcium of at least 65%, with a mean arc of >100°. Above this threshold, the prevalence of lesion-

Table 2. Correlates of Intravascular Ultrasound Target Lesion Calcium

	No. of Pts (% of lesions with IVUS calcium)	p Value	IVUS Arc of Calcium (degrees)*	p Value (ANOVA)
Patient age (yr)		< 0.0001		< 0.0001
21–40	44 (55)		49 ± 61	
41–60	603 (67)		94 ± 100	
61–80	734 (78)		126 ± 111	
>80	61 (94)		186 ± 116	
Angina status		0.0017		0.0002
Stable	1,280 (74)		118 ± 110	
Unstable	162 (62)		81 ± 93	
Diabetes mellitus		0.0020		0.0149
None	1,062 (70)		107 ± 110	
Non-insulin dependent	310 (80)		123 ± 106	
Insulin dependent	70 (57)		98 ± 111	
Vessel		0.8017		0.0119
LMCA	75 (74)		148 ± 128	
LAD	570 (73)		126 ± 117	
LCx	261 (74)		109 ± 103	
RCA	536 (71)		109 ± 108	
Lesion location		0.2526		0.0008
Nonaorto-ostial	1,349 (72)		114 ± 110	
Aorto-ostial	93 (76)		157 ± 127	
Angiographic DS		0.1383		0.1656
≤0.25	50 (65)		91 ± 93	
0.26–0.50	217 (66)		106 ± 118	
0.51–0.75	757 (73)		121 ± 113	
0.76–1.00	418 (74)		115 ± 105	
IVUS lesion CSN		< 0.0001		< 0.0001
≤0.50	54 (26)		17 ± 33	
0.51–0.75	200 (65)		78 ± 84	
0.76–0.90	607 (69)		98 ± 100	
0.91–1.00	581 (70)		121 ± 118	
IVUS ref CSN		< 0.0001		< 0.0001
≤0.50	671 (70)		108 ± 108	
0.51–0.75	771 (76)		138 ± 119	

*Mean ± SD. ANOVA = analysis of variance; CSN = cross-sectional narrowing; DS = diameter stenosis; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; Pts = patients; RCA = right coronary artery; ref = reference.

associated calcium and the size of the arc of calcium did not increase with increasing angiographic diameter stenosis.

Predictors of target lesion calcium. Univariate predictors of the arc of target lesion calcium are shown in Table 2. With the exception of patient age, angina class and a history of diabetes, no clinical variables (e.g., gender, race and other risk factors for coronary artery disease [hypertension, hypercholesterolemia, smoking, family history]) were predictive of target lesion calcium. There was a weak linear correlation ($r = 0.244$, $p < 0.0001$) between patient age and target lesion calcium. With the exception of lesion location and angiographic diameter stenosis, no lesion-associated variables (i.e., bend point, bifurcation, tortuousity) were predictive of target lesion calcium. Importantly, calcification was less in lesions associated with unstable angina.

The variables shown in Table 2 were then entered into the multivariate model. Using multivariate linear regression analysis, patient age ($p < 0.0001$), presence of stable (not unstable) angina ($p < 0.0001$) and ultrasound lesion site and reference segment cross-sectional narrowing (both $p < 0.0001$) were the only independent predictors of the arc of target lesion calcium. The other variables shown in Table 1 were not independent predictors of lesion-associated calcium.

Discussion

The results of the current study indicated that the presence and magnitude of target lesion calcium paralleled the atherosclerotic plaque burden (the cross-sectional narrowing both at the lesion and within the reference segment) as assessed by intravascular ultrasound. The presence and magnitude of target lesion calcium did not parallel the extent of lumen compromise as assessed by quantitative coronary angiography; intermediate lesions had as much target lesion calcium as did

severe lesions. Calcium increased with patient age and was less common in lesions producing unstable coronary syndromes.

Calcium and risk factors for atherosclerosis. Previous pathologic studies (32–36) have shown a correlation between coronary calcium and atherosclerotic plaque volume. It has been suggested (1) that coronary artery calcification does not occur in the absence of coronary atherosclerosis.

By univariate analysis, the only clinical risk factors for coronary calcification in the current study were patient age and non-insulin dependent diabetes. However, when controlled for patient age, non-insulin dependent diabetes was not an independent predictor. Insulin-dependent diabetic patients were less likely to have coronary calcification than either nondiabetic or noninsulin dependent diabetic patients, similar to a recent report by Tuzcu et al. (37). There did not appear to be a plateau to the effect of increasing age on calcium accumulation.

Calcium and disease severity. In a previous study (26) we reported a 73% prevalence of lesion-associated calcium with a mean arc of 115°. These findings were confirmed both in a recent study by Tuzcu et al. (37) as well as in the larger patient and lesion cohort in the current report.

In the current study (other than patient age), the only independent predictors of target lesion calcium were the lesion site and reference segment plaque burden. However, there appeared to be a "saturation point" in the accumulation of lesion-associated calcium. This "saturation point" was reached at a plaque burden >0.75, at which there was a >70% prevalence of lesion-associated calcium with an arc of calcium >120°. It is not known why some severe lesions, even in elderly patients with stable angina, do not contain calcium. However, presumably this finding is related to the different mechanisms of rates of progression of coronary artery disease (38–40). For example, it has been hypothesized that calcium develops after plaque rupture as part of the formation of complicated lesions and that it is rarely seen in small, "soft," cholesterol-rich plaques.

Pathologic and intravascular ultrasound studies have shown (25,41–43) that most of the atherosclerotic plaque volume is contained within the angiographically "normal" reference segments. Intravascular ultrasound studies have shown (25) that reference segment atherosclerosis is typically not calcified. Importantly, the current study demonstrated a relation between reference segment disease and target lesion calcium.

Calcium detected by intravascular ultrasound was not a marker for severe angiographic lumen compromise; and intermediate lesions were as likely to contain significant amounts of target lesion calcium as angiographically severe lesions. (This was also true if ultrasound measures of lumen compromise were used.) As a result, the detection of calcium cannot be used to predict the hemodynamic importance of a lesion. Previous pathologic studies (44) have demonstrated the presence of arterial dilation in direct relation to the cross-sectional area of accumulated atherosclerotic plaque; an absolute reduction in lumen dimensions did not occur until the lesion occupied, on average, an estimated 40% to 50% of the area within the internal elastic membrane. Thus, there will have been extensive target lesion and reference segment atherosclerosis accumulation (and, presumably, lesion calcification) before there is lumen compromise. To support this hypothesis, in the current study there was only a moderate correlation between ultrasound plaque burden and angiographic diameter stenosis. Finally, in a previous report (26), we found a 10% false positive rate for the angiographic detection of target lesion calcification. These findings explain why studies utilizing electron beam computed tomography have found that coronary calcification correlated only moderately well with blinded angiographic findings (14,45,46). In addition, in the current study angiographic lesion characteristics, such as vessel tortuosity; eccentricity; or bend-point, branch-point or ostial (other than aorto-ostial) lesion location, were not predictive of lesion calcification.

The current study also shows that there was a weak but significant interlesional correlation in the arc of calcium. Presumably, this correlation reflected the influence of patient-related variables (i.e., age) and the diffuseness of the atherosclerotic disease process. However, there was still a significant between-lesion variation (Table 1). This variation may help to explain why there is between-lesion independence in the acute and chronic responses to catheter-based interventions (47).

Calcium and cardiac events. Margolis et al. (48) found that patients with angiographic calcium had an 8-year mortality rate that was four times that of patients without angiographic calcium. Detrano et al. (14) found that patients with an electron beam tomographic calcium score greater than the median were six times more likely to have a coronary heart disease-related event (death or myocardial infarction) than patients with a score below the median; furthermore, increasing scores were associated with an increasing odds ratio of an event. Similarly, in asymptomatic self-referred patients Arad et al. (15) found that a high electron beam tomographically derived coronary artery calcium score (≥100) increased the likelihood of subsequent cardiac events (death, myocardial infarction, bypass graft surgery, angioplasty or stroke) by a factor of ≥20.

There are a number of reasons why calcium may be a marker for cardiac events. Demer et al. (49) have suggested that calcification may actively contribute to the susceptibility of plaque rupture. However, in a previous intravascular ultrasound study, Hodgson and co-workers (50,51) indicated that lesions in patients presenting with unstable coronary syndromes are more often soft, contain fewer calcified and mixed plaque and have fewer intralesional calcium deposits than lesions in patients with stable angina. Similarly, in the current study, there was less calcium in culprit lesions found in patients with unstable coronary syndromes. (We also tended to find less calcium in the reference segments of these lesions: 28 ± 69° vs. 42 ± 81°, p = 0.0947.) Thus, it is unlikely that calcium participates in the pathophysiologic mechanisms of unstable coronary syndromes.

Alternatively, the overall atherosclerotic plaque volume has been shown (41,52–54) to be a strong predictor of mortality. In

the current study, all the evidence indicates that calcium is merely a marker for the atherosclerotic plaque burden. A greater overall plaque volume, combined with the heterogeneity of the atherosclerosis disease process, increases the likelihood of potentially unstable lesions. Thus, calcium may be a marker for future cardiac events because it is a marker for extensive atherosclerosis.

Limitations of the study. This was a retrospective analysis of a large group of patients referred for diagnostic evaluation or for intervention. All the patients had coronary atherosclerosis; therefore, this study could not address the issue of coronary calcification in the absence of coronary artery disease. Some lesions could not be crossed with the ultrasound catheter before intervention; in our experience this was usually a lesion with both marked lumen compromise and extensive calcification. The present study used patient age and plaque burden as surrogates for duration of the atherosclerotic disease process. Presumably, calcium accumulation is dependent on disease chronicity.

In addition, there may have been bias in the selection of "culprit" lesions for the current study. This bias may be reflected by the relative proportion of culprit versus nonculprit treated lesions, treated lesions associated with stable versus unstable angina and nontreated lesions. For example, lesions associated with unstable angina had less calcium than lesions associated with stable angina; and nontreated lesions had less calcium than treated lesions. Furthermore, the ages of the treated lesions were not known.

Conclusions. Intravascular ultrasound analysis shows that coronary calcification is a marker for atherosclerotic plaque burden but not for significant lumen compromise. Coronary calcification increases with increasing patient age and is less common in unstable lesion subsets. These findings may explain recent reports indicating that the noninvasive detection of coronary calcium is predictive of future cardiac events.

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